Antiarrhythmic effects of dantrolene in human diseased cardiomyocytes.


Abstract

BACKGROUND: Cardiac type 2 ryanodine receptors (RyR2s) play a pivotal role in cellular electrophysiology and contractility. Increased RyR2-mediated diastolic sarcoplasmic reticulum (SR) Ca\(^{2+}\) release is linked to heart failure (HF) and arrhythmias. Dantrolene, a drug used for the treatment of malignant hyperthermia, is known to stabilize RyRs in skeletal muscle.

OBJECTIVE: The purpose of this study was to investigate the effects of dantrolene on arrhythmogenic triggers and contractile function in human atrial fibrillation (AF) and HF cardiomyocytes (CM).

METHODS: Human CM were isolated from either patients with HF (ventricular) or patients with AF (atrial), and Ca\(^{2+}\) imaging, patch-clamp, or muscle strip experiments were performed.

RESULTS: After exposure to dantrolene, human atrial AF and left ventricular HF CM showed significant reductions in proarrhythmic SR Ca\(^{2+}\) spark frequency and diastolic SR Ca\(^{2+}\) leak. Moreover, dantrolene decreased the frequency of Ca\(^{2+}\) waves and spontaneous Ca\(^{2+}\) transients in HF CM. Patch-clamp experiments revealed that dantrolene significantly suppressed delayed afterdepolarizations in HF and AF CM. Importantly, dantrolene had no effect on action potential duration in AF or in HF CM. In addition, dantrolene had neutral effects on contractile force of human isometrically twitching ventricular HF trabeculae.

CONCLUSION: Our study showed that dantrolene beneficially influenced disrupted SR Ca\(^{2+}\) homeostasis in human HF and AF CM. Cellular arrhythmogenic triggers were potently suppressed by dantrolene, whereas action potential duration and contractility were not affected. As a clinically approved drug for the treatment of malignant hyperthermia, dantrolene may be a potential antiarrhythmic drug for patients with rhythm disorders and merits further clinical investigation.
ANTIARRHYTHMIC EFFECTS OF DANTROLENE IN HUMAN DISEASED CARDIOMYOCYTES.

KEYWORDS: Antiarrhythmic agent; Arrhythmia; Atrial fibrillation; Dantrolene; Electrophysiology; Heart failure; Ryanodine receptor; Sarcoplasmic reticulum Ca(2+) leak

Comment in
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